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METABOLIC SYNDROME: WHERE IT ALL BEGINS

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The title begets the issue: Is there such an entity as metabolic syndrome, how did the syndrome generate so much interest and is it really useful clinically to predict the absolute risk of Diabetes and cardiovascular disease?

The concept of Metabolic Syndrome first took the attention of the scientific medical community when Reaven published in 1988 the concept that insulin resistance is the common physiological abnormality linking the abnormal glucose tolerance, central obesity, hypertension, and dyslipidemia, calling it a metabolic syndrome of physiological interest. The subsequent onslaught of publications however treated it as a clinical or epidemiological entity with various definitions over the next two decades and linking it to the relative risk of developing diabetes or cardiovascular event. This was not what it was meant to be, as the subsequent data generated showed that each entity of the syndrome e.g. hypertension, central obesity, confers a certain risk and the sum of the entities do not confer any greater risk of CVD. The Metabolic Syndrome also did not cater for more important risk factors found in the Framingham Risk calculation such as age, gender, LDL cholesterol, etc. Because of differing definitions of the Metabolic Syndrome by WHO, IDF, ADA, NCEP ATP 111 etc, comparisons for epidemiological significance was not always possible. Thus the Metabolic Syndrome has now lost its luster!

But "where it all begins" is really what Reaven wanted to stimulate research interest in: Is insulin resistance the common denominator that links all the 4 features of the syndrome. If so, what causes this insulin resistance? How do we link insulin resistance to central obesity? Which comes first? Central obesity causing insulin resistance or vice versa? Similarly how is it linked to hyperinsulinemia and subsequent development of diabetes? How is it linked to dyslipidemia? And hypertension? And also in women, with polycystic ovaries?

Our interest has always been in this fascinating physiological misnomer. One possible common pathway could be a genetically determined abnormality in handling the endogenous glucocorticoid steroid cortisol by the abdominal fat tissue, resulting in a dysfunction of the hypothalamo-pituitary-adrenal axis at the tissue level. Glucocorticoid steroids in excess will cause dyslipidemia similar to that seen in Metabolic Syndrome. Similarly excess steroids cause central obesity, insulin resistance and diabetes, hypertension and polycystic ovaries...a clinical entity called Cushing's disease. Metabolic Syndrome however does not have the other features of Cushing's syndrome of proximal myopathy, osteoporosis, protein catabolism resulting in thin skin with easy bruising, and suppression of the lymphoid system involved with humoral and cellular immunity. Clearly thus it is a "limited form" of Cushing's syndrome!

Our ideas that this could be a variety of steroid hormone dysfunction at the abdominal fat level stems from the discovery of the enzyme 11 beta hydroxysteroid dehydrogenase which reversibly converts active hormone cortisol to inactive cortisone. This enzyme is particularly important in the kidneys where it exists as the 11 HSD type 2 enzyme and is dependent on the co-factor NADPH. It "protects" the kidneys from the excess cortisol found in the circulation, from acting on the mineralocorticoid receptor, competing with aldosterone in regulating salt balance by the kidney tubules. In individuals of families that lack this type 2 form of 11 HSD, the excess cortisol causes hypertension, so called pseudohyperaldosteronism or Cushing's disease of the kidneys. Only the kidney function was disturbed. Similarly, the testes and ovaries are protected against excess steroids during stress which could inhibit the function of Luteinizing hormone receptors and causing anovulation by the ovaries or lower testosterone levels during stress. Similarly during stress, ACH is stimulated with increase cortisols throughout the 24 hour period with loss of the circadian rhythm, and causing increase blood pressure even during sleep...an early feature of hypertension in "Metabolic Syndrome". Similarly, excess steroids during stress causes increase insulin resistance, and at times frank hyperglycemia called "Stress Hyperglycemia" not amounting to diabetes. Clearly if an abnormal 11HSD enzyme is found at the abdominal fat tissue and/or ovaries and/or the hypothalamus, then this could cause a predisposition to abnormally over production of active cortisols in these tissues leading to the features seen in metabolic syndrome. The hypothesis is not confined to 11 HSD alone...there are many examples in physiology, such as Vitamin D Resistant Rickets, in pseudohypoparathyroidism, familial Conns Syndrome, etc. It is also exemplified by the fact that enzymes in the body have many isotypes such as found for Phosphodiesterase Enzymes that break down cyclic AMP/GMP. The type 5 PDE is found only in the penis erectile tissue...a fact made use of in Viagra etc.

The enzyme can be inhibited by ligands such as glycyrrhizic acid or GCA derived from the Glycyrrhia Species plants used in traditional medicines and preservatives such as Assam Boi. Using this ligand, we could show that many of the effects of excess cortisol in abdominal fat and liver etc in animals with induced obesity can be reversed and insulin sensitivity is increased. In genetically engineered rats with deficiency of 11 HSD, the insulin resistance and dyslipidemias were absent even when the animals were stressed and overfed.

Clearly the environment must play a role in the development of diabetes, hypertension and obesity. The metabolic genetic marker may be present even before the onset of the frank diabetes...by insulin resistance even with normal sugars, and the dyslipidemia of high triglyceride and low HDL cholesterol. But when the environment provides for extra calories and at the same time increase stress levels such that the circadian rhythm of cortisol is lost, then the effect of the abnormal 11 HSD would manifest. Thus the increase in hypertension and obesity and diabetes in westernized rapidly developing countries like Malaysia and China and India. The beginning, could just be abnormal 11HSD in fat tissues...